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Screening for spontaneous preterm birth

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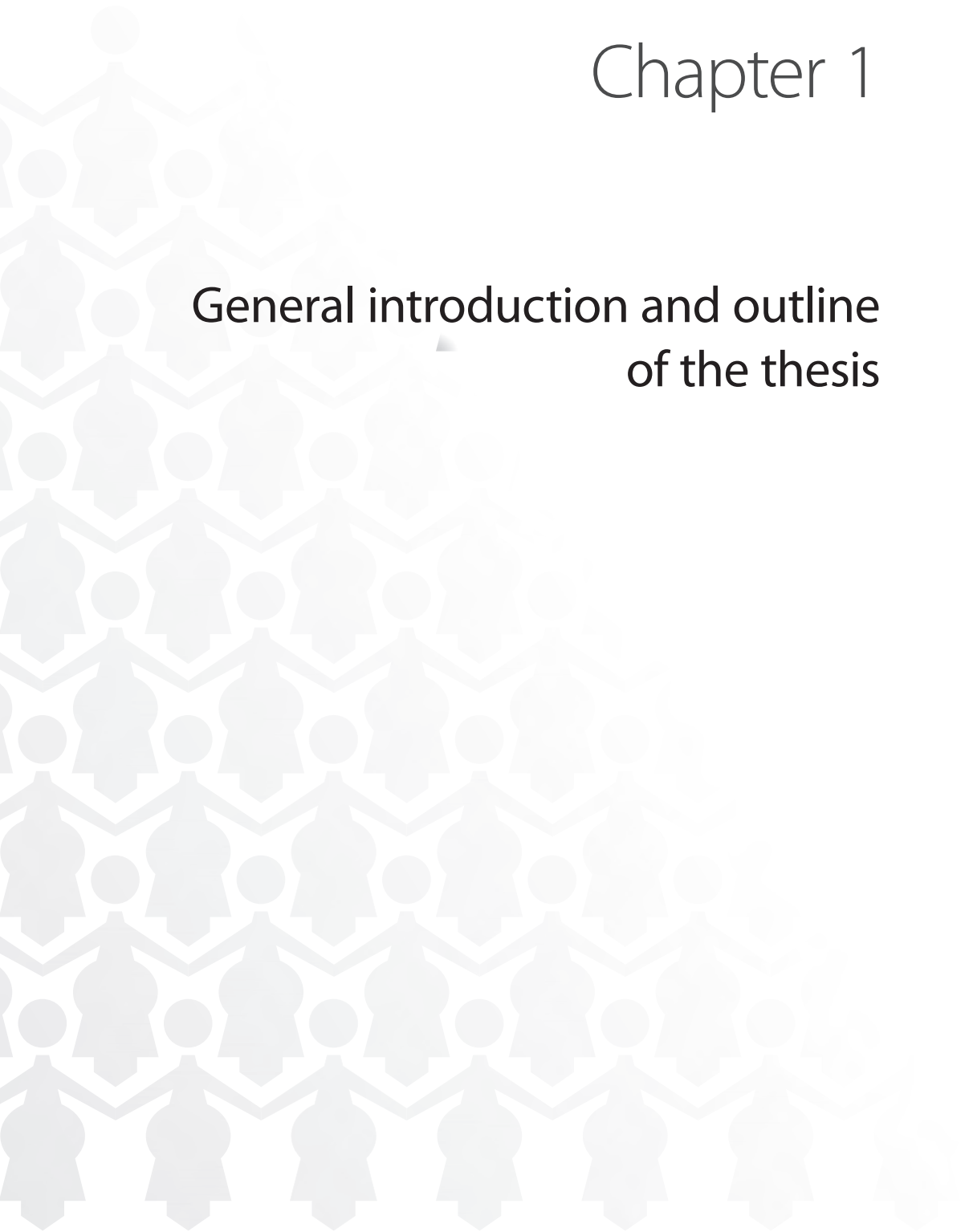
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Chapter 1

General introduction and outline of the thesis



Preterm birth, the problem

Preterm birth is traditionally defined as a delivery before 37 completed weeks of gestation. Approximately 15 million neonates are born premature worldwide yearly, implying a rate of one out of ten neonates¹. The rate of preterm birth is still rising². Preterm birth is the leading cause of mortality in new-borns². Long-term morbidity in survivors comprises of learning disabilities, hearing loss, behavioural problems and visual disturbances². Inequalities of prevalence and survival rates vary considerably. The prevalence of preterm birth is the highest in Africa and South Asia.

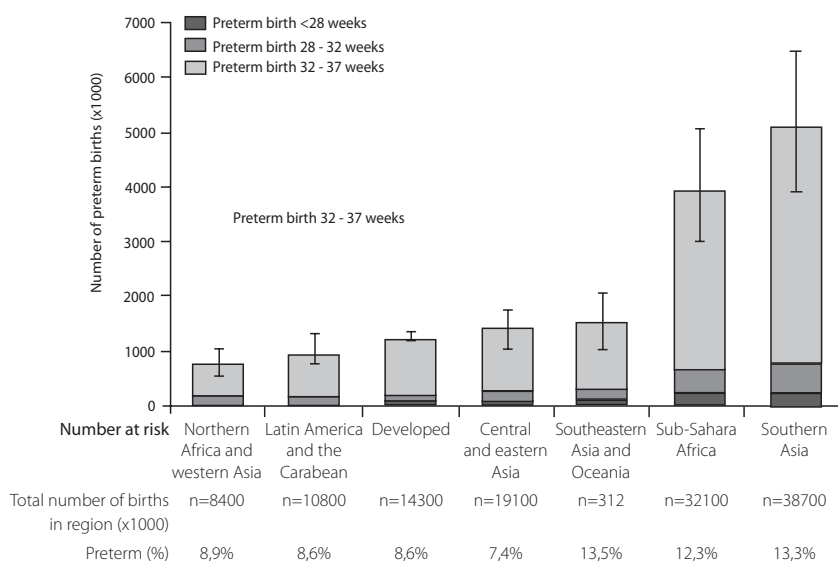


Figure 1. National, regional and worldwide estimates of preterm birth rates in the year 2010 for selected countries: a systematic analysis and implications. Blencowe *et al.* Lancet 379(9832): 2162-2172. By permission.

In developed countries the preterm birth rate is about 8% of all pregnancies¹. In the Netherlands, perinatal mortality was 9.7 per 1000 total births. Preterm births (> 22.0 weeks and < 37.0 weeks) accounted for 75.3 % of all perinatal mortality with a mortality risk of 82.6 per 1000 births^{3,4}. Short-term and long-term effects of preterm birth on society and health systems are profound⁵. Reducing the burden of child mortality due to preterm birth, is therefore one of the eight Millennium Development Goals⁶. Hence, prevention of preterm birth is essential to reduce the high mortality and the considerable risk of lifelong impairment⁷.

Perinatal mortality in The Netherlands

Preterm birth is one of the most common causes of perinatal death in the Netherlands. Since the publication of the Euro-Peristat report in 2008, which compared perinatal death rates in different countries in Europe, the Netherlands was forced to attempt to understand the relative high perinatal mortality (1% of all births yearly). Factors that may contribute, are patient characteristics, social and environmental factors and the organisation of the health care system.

The organisation of the Dutch obstetric health care system is different from that in other developed countries. In the Netherlands, care is differentiated in low-risk and high-risk women during pregnancy and delivery⁸. Women with low-risk pregnancies are supported by primary obstetric care providers (midwives and midwifery active general practitioners). In the occurrence of complications or an expected risk on complications during pregnancy or delivery, referral to an obstetrician takes place. Threatened preterm labour and post-date pregnancies are examples for referral⁹.

Who is at risk for preterm birth?

Preterm birth can occur spontaneously or for medical reasons (iatrogenic preterm birth). In this thesis we focus on *spontaneous* preterm birth. The two pillars in the strategy to reduce preterm birth are prevention and care for women who present with threatened preterm labour. The underlying pathophysiology of spontaneous preterm birth is not completely understood and has probably multiple causes, which makes prevention strategies challenging.

Care for women with (threatened) preterm birth include interventions such as tocolysis, bed rest or placement of a cervical cerclage. These measures have limited effectiveness¹⁰⁻¹². The only intervention proven to be beneficial to improve neonatal outcome so far, is the administration of corticosteroids¹³. Consequently, prevention of the onset and identification of the women at risk for preterm birth is essential. The most important symptom of preterm labour is a premature pathological cervical ripening, characterised by a shortening and dilatation of the cervix, which is usually accompanied with increased uterine activity¹⁴.

Various risk factors and methods of screening have been identified. The most important risk factor which predicts preterm birth, is a history of premature birth¹⁵. Nulliparous women do, however, not benefit from this knowledge. Therefore, most preterm births occur in women initially classified as low risk. A second important risk for preterm birth is a multiple pregnancy. These pregnancies, however, are not the scope of this thesis. In this thesis we focus on singleton pregnancies.

Methods of screening for preterm birth include testing for fetal fibronectin and ultrasonographic cervical length measurement.

Currently, cervical length measurement between 20-24 weeks gestation is thought to be the best method of screening for premature birth¹⁶⁻¹⁸. A strong association between a short cervix in the second trimester and a subsequent premature birth has been shown by several studies¹⁶⁻¹⁸. Thus, in a low-risk population of women (defined as nulliparous women and women without a history of preterm birth), women with a short cervical length between 20-24 weeks of gestation are at risk. A screening program is only justified according to the international criteria of Wilson and Jungner (1968), which were updated by the WHO in 2008, if an effective intervention is available^{19,20}.

Cervical length

Ultrasonographic cervical length measurement is most often used in the clinical setting in women who present with premature contractions. The aim of the measurement is to differentiate which woman will actually give birth prematurely. If the cervical length is above 30 mm in these women, they have a low risk to have a pregnancy complicated by preterm labour^{15,21}.

The discriminating ability of cervical length measurement is of great value for timely transfer to a university hospital and corticosteroid treatment for fetal lung maturation in case of an imminent premature birth. If these measures are taken in time, improved neonatal outcome can be obtained.

Besides the use of cervical length measurement in women with threatened premature labour, it can also be used for prediction of preterm birth in the absence of contractions. A strong association between a short cervix in the second trimester and a subsequent premature birth is shown by several studies¹⁶⁻¹⁸. At 20-24 weeks of gestation the average cervical length is within a range of 35-38 mm, measured in singleton pregnancies¹⁶⁻¹⁸. In 1-2 % of the women a cervical length of less than 15 mm is found, which carries a risk for premature birth of approximately 30%. In 8-10% of women, a cervical length less than 25mm is found, which carries a risk for premature birth of approximately 5%^{12,17,18}. The relative risk of preterm delivery was found to increase as the cervical length decreased¹⁸. Because shortening of the cervical length is associated with preterm birth, the question raises whether a long cervical length is associated with post-term delivery and increased caesarean section rate.

Ultrasonographic examination of the cervix

From an anatomical point of view the cervix is the area where the uterine walls come together to form the narrow end of the uterus, which ends in the vagina.

During pregnancy the cervix changes and it will elapse and dilate during birth.

The most reliable method to measure the cervix is transvaginal ultrasound²²⁻²⁴.

A technically correct cervical length measurement is performed with an empty bladder with the transvaginal probe placed in the anterior fornix. The examiner has to prevent pressure on the cervix by pulling back the probe slightly. This will result in an image with a more or less equally thick anterior and posterior lip of the cervix.

The exact mid-sagittal section of the cervix visualises the endocervical mucosa, which should prosecute the whole distance between amnion and external os.

After visualisation of the cervix, the examiner has to wait 2 to 3 minutes for any contractions to be detected. Some pressure can be exerted on the fundus to mimic possible shortening by a contraction²⁵. The endocervical mucosa is an echogenic line of amnion to the external os. The finding of a discernible echolucent stripe-shaped center, which is the mucus of the cervix, is of no clinical significance.

The calipers must be placed to measure the distance between the internal os and the external os (Figure 2). The cervix is often curved. It is not clinically relevant if the measurement is done in one or several tempos²⁶. A curved cervix is always long enough, a short cervix is always straight²⁷. If there is a difference between several measurements, the shortest measurement is usually taken as the clinically relevant measurement.

Funnelling is defined as the bulging of the membranes in the internal os. When a cervix is short, funnelling is usually present (Figure 3). Funnelling is not clinically relevant, as it is the shortened cervical length that is the predictive factor for preterm birth²⁷. Research shows that the measurement of the cervix is a valid measurement, intraobserver and interobserver variability is small²⁸⁻³⁰.

Transvaginal ultrasound is perceived acceptable by women³¹. In women undergoing cervical length measurement 94% experienced little or no discomfort and 98% experienced no or little embarrassment during the measurement³¹. The cervical length measurement itself should be performed using similar technique, to ensure uniformity.

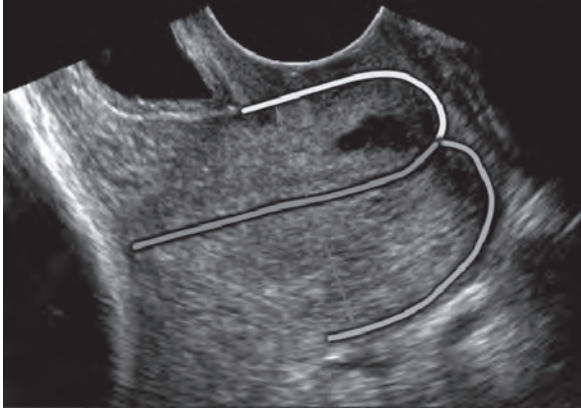


Figure 2 Image of a cervix with the anterior and posterior cervix and the cervical canal in lining.

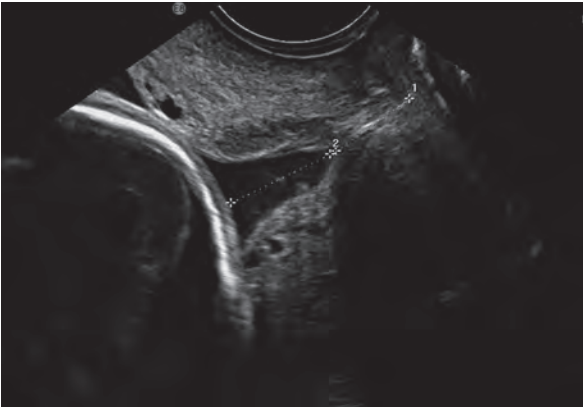


Figure 3 Image of a cervical length measurement with the calipers placed on the internal and external os.

Apart from technical variation in cervical length measurement, several other factors might play a role in the data on cervical length, including parity, anthropometric characteristics, time of the day, unknown uterine activity, infection and bleeding during pregnancy.

Treatment to prevent preterm birth

In the first trimester of pregnancy progesterone plays an important role by endometrial proliferation and sustaining early pregnancy. Progesterone was discovered in the late 20s. It is mainly produced by the corpus luteum in pregnancy. The production is taken over by the placenta after 12 weeks of pregnancy.

Based on these data, it has been postulated that progesterone as a substance might be used to prolong pregnancy in case of an imminent premature delivery. In animal models, a drop in progesterone levels was observed before the delivery occurred³². These findings could, however, not be confirmed in humans and the use of progesterone was abandoned for years.

In the 60s a revival of the progesterone theory took place. It was found that a relative drop of progesterone levels had an effect of rising oxytocin and prostaglandin levels³³.

Another important finding was the use of mifepristone (a progesterone antagonist) in termination of pregnancies. Mifepristone induced uterine contractions. This also confirmed the theory that progesterone supports the latter half of pregnancy³³.

Progesterone appears to be important in maintaining uterine quiescence in the latter half of pregnancy³⁴⁻³⁶. It has been shown that progesterone limits the production of stimulatory prostaglandins and inhibits the expression of contraction-associated protein genes within the myometrium, including ion channels, oxytocin and prostaglandin receptors, and gap junctions³⁷. Recent studies in a combined high and low-risk population have shown that progesterone reduces the number of premature births in women with a short cervical length at mid gestation³⁸⁻³⁹. Progesterone already seemed to be effective in women with a history of premature birth⁴⁰. A number of studies describe safety of progesterone during pregnancy. These studies comprise about 2000 neonates in total. No difference in the number of congenital anomalies were found directly after birth. In follow up studies (up to 48 months), no differences were found between children who were exposed to progesterone in utero and who weren't⁴¹⁻⁴⁴.

Outline and aims of this Thesis

In this thesis studies on spontaneous preterm birth are presented. The main objective was to identify women at risk for preterm birth in a low-risk population and assess the effect of progesterone for the prevention of preterm birth in women who had a short cervical length. The separate aims of this thesis are given below.

Part one: Preterm birth; the problem

- Outline of the risk factors for preterm birth in a review of literature (**chapter 2**).

Part two: Who is at risk for preterm birth?

- Demonstrate the Protocol of Triple P *screening* and *treat* study (**chapter 3**).
- Investigate, among women with low-risk pregnancies, the capacity of cervical length measurement to identify women at increased risk for preterm birth. (**chapter 4**).
- Study the association between adverse perinatal outcome of spontaneous preterm births and the level of care at time of labour onset and delivery. (**chapter 5**).

Part three: Ultrasonographic examination of the cervix

- Assess the effect of a cervical length e-learning module on the quality of cervical length measurements in asymptomatic low-risk pregnancies. (**chapter 6**).
- Statistically analyse the distribution of cervical length measurements, and review the effect of a pre-defined cut-off value (**chapter 7**).
- Assess the relationship of mid-trimester cervical length and maternal characteristics. (**chapter 8**).
- Assess the possible relationship between mid-trimester cervical length and its correlation with post-term delivery and intrapartum caesarean delivery. (**chapter 9**).

Part four: Treatment to prevent preterm birth

- Evaluate the effectiveness of vaginal progesterone in reducing adverse neonatal outcome due to preterm birth, in low-risk pregnant women with a mid-trimester short cervical length. (**chapter 10**).

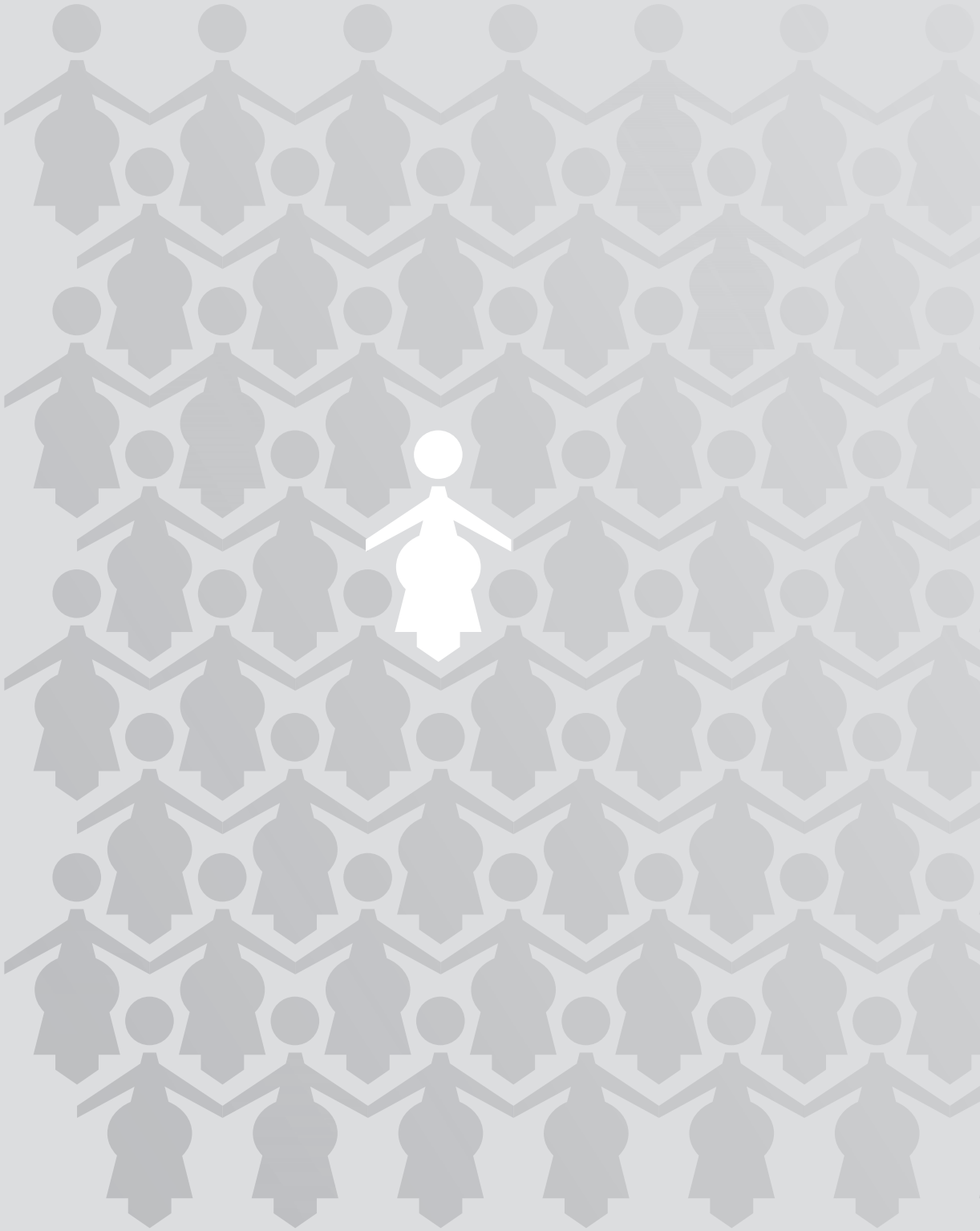
Part five: Women's preference

- Study the preference of pregnant women regarding cervical length measurement and treatment with progesterone in relation to preterm birth (**chapter 11**).

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Part one:

Preterm birth; the problem

